METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims benefit of priority to U.S. Provisional application Ser. No. 61/093,234, filed Aug. 29, 2008, which is incorporated herein by reference in its entirety. This application is also related to the U.S. provisional patent application entitled "Treating special populations having liver disease with nitrogen-scavenging compounds," naming Sharron Gargosky as inventor, Ser. No. 61/048,830, filed on Apr. 29, 2008.

TECHNICAL FIELD

This invention relates to treatment of patients with nitrogen retention states, in particular urea cycle disorders (UCDs) and cirrhosis complicated by hepatic encephalopathy (HE), using administered compounds that assist in elimination of waste nitrogen from the body. The compounds can be orally administered small-molecule drugs, and the invention provides methods for delivering these compounds and selecting suitable dosages for a patient.

BACKGROUND ART

Drug dosing is usually based upon measurement of blood levels of the active drug species in conjunction with clinical assessment of treatment response. However, the present invention is based on evidence that for certain prodrugs of phenylacetic acid (PAA), measuring the blood level of the prodrug (e.g. PBA) or of PAA formed from it is unreliable. In addition, assessment of treatment effect by measuring levels of ammonia in the blood is inconvenient, because it requires withdrawing multiple blood samples under carefully controlled conditions. Because blood ammonia levels are affected by various factors including dietary protein, they also fail to provide a direct measure of how much ammonia the drug is mobilizing for elimination. The invention demonstrates that prodrugs of phenylbutyric acid (PBA) behave similarly to sodium PBA, in that measuring PBA levels is unreliable for assessing their effectiveness. This invention provides a novel method for dosing in patients with nitrogen retention states, in particular patients with liver disease and clinical manifestations of hepatic encephalopathy and patients with UCDs. It is particularly applicable to prodrugs that liberate or are metabolized to form phenylacetic acid, i.e., prodrugs of PAA, and those prodrugs that are metabolized to form PBA.

Hepatic encephalopathy refers to a spectrum of neurologic signs and symptoms which frequently occur in patients with cirrhosis or certain other types of liver disease.

Urea cycle disorders comprise several inherited deficiencies of enzymes or transporters necessary for the synthesis of urea from ammonia. The urea cycle is depicted in FIG. **1**, which also illustrates how certain ammonia-scavenging drugs act to assist in elimination of excessive ammonia. The enzymes including their Enzyme Commission (EC) numbers and modes of inheritance include the following:

- Carbamyl phosphate synthetase (CPS; EC Number 6.3.4.16; autosomal recessive),
- ornithine transcarbamylase (OTC; EC Number 2.1.3.3; X-linked),
- argininosuccinate synthetase (ASS; EC Number 6.3.4.5; autosomal recessive),
- argininosuccinate lyase (ASL; EC Number 4.3.2.1; autosomal recessive),
- arginase (ARG; EC Number 3.5.3.1; autosomal recessive), and
- N-acetyl glutamine synthetase (NAGS 1; EC Number 2.3.1.1; autosomal recessive)

Mitochondrial transporter deficiency states which mimic many features of urea cycle enzyme deficiencies include the following:

- Ornithine translocase deficiency (hyperomithinemia, hyperammonemia, homocitrullinuria or HHH Syndrome)
- Citrin (aspartate glutamate transporter) deficiency

The common feature of UCD and hepatic encephalopathy that render them treatable by methods of the invention is an accumulation of excess waste nitrogen in the body, and hyperammonemia. In normal individuals, the body's intrinsic capacity for waste nitrogen excretion is greater than the body's waste nitrogen production, so waste nitrogen does not accumulate and ammonia does not build up to harmful levels. For patients with nitrogen retention states such as UCD or HE, the body's intrinsic capacity for waste nitrogen excretion is less than the body's waste nitrogen production based on a normal diet that contains significant amounts of protein. As a result, nitrogen builds up in the body of a patient having a nitrogen retention disorder, and usually results in excess ammonia in the blood. This has various toxic effects; drugs that help eliminate the excess ammonia are an important part of an overall management strategy for such disorders.

To avoid build-up of ammonia to toxic levels in patients with nitrogen retention states, dietary intake of protein (a primary source of exogenous waste nitrogen) must be balanced by the patient's ability to eliminate excess ammonia. Dietary protein can be limited, but a healthy diet requires a significant amount of protein, particularly for growing children; thus in addition to controlling dietary protein intake, drugs that assist with elimination of nitrogen are used to reduce ammonia build-up (hyperammonemia). The capacity to eliminate excess ammonia in treated patients can be considered the sum of the patient's endogenous capacity for nitrogen elimination (if any) plus the amount of additional nitrogen-elimination capacity that is provided by a nitrogen scavenging drug. The methods of the invention use a variety of different drugs that reduce excess waste nitrogen and ammonia by converting it to readily-excreted forms, such as phenylacetyl glutamine (PAGN). In some embodiments, the invention relates to methods for determining or adjusting a dosage of an oral drug that forms PAA in vivo, which is converted into PAGN, which is then excreted in urine and thus helps eliminate excess nitrogen.

Based on prior studies in individual UCD patients (e.g. Brusilow, *Pediatric Research*, vol. 29, 147-50 (1991); Brusilow and Finkelstien, *J. Metabolism*, vol. 42, 1336-39 (1993)) in which 80-90% of the nitrogen scavenger sodium phenylbutyrate was reportedly excreted in the urine as PAGN, current treatment guidelines typically either assume complete conversion of sodium phenylbutyrate or other PAA prodrugs to PAGN (e.g. Berry et al., *J. Pediatrics*, vol. 138, S56-S61 (2001)) or do not comment on the implications of incomplete conversion for dosing (e.g. Singh, Urea Cycle Disorders Conference Group '*Consensus Statement from a Conference for the Management of Patients with Urea Cycle Disorders', Suppl to J Pediatrics*, vol. 138(1), S1-S5 (2001)).

Current treatment guidelines recommend 4 times per day dosing, based on the fact that PBA is absorbed rapidly from the intestine when administered in the form of sodium PBA